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Background Parenchymal Enhancement of the Contralateral Normal Breast: Association with Tumor Response in Breast Cancer Patients Receiving Neoadjuvant Chemotherapy[1]

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Abstract

PURPOSE: This study investigated the association between background parenchymal enhancement (BPE) and pathologic response to neoadjuvant chemotherapy (NAC). *METHODS:* A total of 46 patients diagnosed with invasive breast cancer were analyzed. Each patient had three magnetic resonance imaging (MRI) studies, one pre-treatment and two follow-up (F/U) MRI studies. BPE was measured as the averaged enhancement of the whole fibroglandular tissues. The pre-treatment BPE and the changes in the F/U MRI were compared between patients achieving pathologic complete response (pCR) *versus* those not. Subgroup analyses based on age, estrogen receptor (ER), and human epidermal growth factor receptor 2 (HER2) status of their cancers were also performed. *RESULTS:* The pre-treatment BPE was higher in the pCR group than that in the non-pCR group. Compared to baseline, BPE at F/U-1 was significantly decreased in the pCR group but not in the non-pCR group. In subgroup analysis based on age, these results were seen only in the younger group (<55 years old), not in the older group (≥55 years old). Older patients had a significantly lower pre-treatment BPE than younger patients. In analysis based on molecular biomarkers, a significantly decreased BPE at F/U-1 was only found in the ER-negative pCR group but not in the non-pCR, nor in the ER-positive groups. *CONCLUSIONS:* A higher pre-treatment BPE showing a significant decrease early after starting NAC was related to pCR in pre/peri-menopausal patients.

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Introduction

Dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) is widely used for the diagnosis of breast cancer. The amount of contrast agents that can reach the normal fibroglandular breast tissue is an indicator of blood perfusion to the normal tissue, referred to as background parenchymal enhancement (BPE), which can be evaluated qualitatively [1,2] or measured quantitatively [3]. Previous studies have demonstrated that BPE is affected by age, physiologic hormonal status, and hormonal therapy [4–6]. It was noted that BPE in pre-menopausal women is altered over the women's menstrual cycle [7,8].

Most published studies about BPE focused on the diseased breast harboring breast cancer. It was found that BPE may affect the diagnostic performance of breast MRI [9,10]. Because of its clinical

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impact on the diagnosis, BPE and its descriptors have been added to the recent updates and revision of The Breast Imaging Reporting and Data System (BI-RADS) breast MRI lexicon [11]. Several studies also noted that BPE surrounding primary breast tumors was associated with response to neoadjuvant chemotherapy (NAC) and prognosis [12], as well as with recurrence-free survival in patients with ductal carcinoma *in situ* after breast conservation surgery [13]. However, because of the presence of cancer, the measurement of BPE in the diseased breast will be strongly dependent on the location where the measurement was made from or the placement of region of interest (ROI).

As most DCE-MRI studies were performed bilaterally on breast cancer patients, the BPE in the contralateral normal breast could be measured, and on the basis of breast symmetry, the measured BPE in this way could reflect the normal tissue enhancements in the diseased breast. A recent study comparing the difference of BPE in the normal breasts between pre-menopausal and post-menopausal women found that BPE was higher in pre-menopausal than in post-menopausal women, and a decreased BPE after receiving NAC was found in pre-menopausal, not in post-menopausal, women [14]. These results suggested that the difference was most likely coming from ovarian function and the suppression due to chemotherapy [14]. Since the BPE is related to blood perfusion (thus affecting delivery of therapeutic agent) and likely ovarian function (thus affecting the hormone level), it may also affect the treatment response of breast cancer to NAC. So far, there has been no report to investigate this relationship yet.

In the present study, we measured BPE in the contralateral normal breasts of NAC patients who achieved pathologic complete response (pCR) and those not achieving pCR (non-pCR). The pre-treatment BPE and the changes during NAC between the pCR and non-pCR groups were compared. In addition, we performed subgroup analysis by separating patients based on age, the estrogen receptor (ER), and human epidermal growth factor receptor 2 (HER2) of their cancers. The BPE between patients with ER-positive and ER-negative cancers and that between patients with HER2-positive and HER2-negative cancers were also compared.

Materials and Methods

Subjects

The study is a retrospective analysis of prospectively enrolled breast cancer patients who were elected to receive NAC treatment before surgery from 2002 to 2006. The study was approved by the Institutional Review Board and was The Health Insurance Portability and Accountability Act (HIPAA) compliant. All participants gave written informed consent. A total of 52 subjects who had one pre-treatment baseline MRI and at least two follow-up (F/U) MRIs while undergoing NAC regimen and received surgery after NAC were identified. Six patients were excluded from the analysis because of the following reasons: patients with contralateral breast lesions, patients with extremely fatty breast (< 5% breast density as measured in MRI), and patients with poor MR image quality in any of their three MRIs. Of remaining 46 subjects, 40 had invasive ductal cancer (IDC), 5 had infiltrating lobular cancer (ILC), and one had mixed IDC and ILC. The age of patients at the start of study ranged from 31 to 77 years old [50 ± 11 (mean ± SD), median 49 years]. The one-dimensional tumor size in baseline MRI ranged from 0.5 to 9.9 cm [4.1±2.3cm (mean ± SD), median 3.4 cm].

The pathologic response was determined based on the examination of surgical specimen after completing NAC. pCR was defined as the absence of malignant cancer cells. Non-pCR was defined as the presence of residual cancer cells in pathology. For subgroup analysis based on age, patients were separated into pre/peri-menopausal (< 55 years old, $N = 32$) and post-menopausal groups (≥ 55 years old, $N = 14$). For the whole group, and each age and biomarker subgroup (ER-positive cancer, ER-negative cancer, HER2 receptor–positive cancer, and HER2 receptor–negative cancer), BPE in patients of the pCR and non-pCR groups were compared.

NAC Treatment Protocol

The chemo-regimen used at our institution from 2002 to 2006 consisted of two to four cycles of dose-dense AC (doxorubicin and cyclophosphamide, one cycle every 2 weeks) followed by taxane regimen (TCa ± H, paclitaxel and carboplatin with Herceptin for HER2/neu-positive patients). After the patient received two cycles of AC, based on clinical examination and ultrasound findings, the oncologist determined the response and decided whether she should go on to receive additional two cycles of AC (if responding well) or be switched to the second regimen (if not). The first F/U-MRI was performed after one cycle ($N = 19$) or two cycles ($N = 27$) of AC. The second F/U-MRI was performed after receiving four cycles of AC ($N = 25$) or after receiving two cycles AC plus three weekly second-line taxane-based regimen ($N = 21$).

MRI Study Protocol

All MRI studies were performed on a 1.5-T Philips Eclipse MR scanner (Philips Medical System, Best, Netherlands) using a dedicated bilateral breast coil with the patient in the prone position. The DCE-MRI was acquired using a three dimensional (3D) gradient echo pulse sequence (RF-FAST) with repetition time (TR)/echo time (TE) = 10/3.6 milliseconds, flip-angle = 20°, 32 bilateral-axial partitions covering both breasts with 4-mm thickness each, field of view (FOV) = 32 to 38 cm, and acquisition matrix = 256 × 128. Sixteen dynamic frames (repetitions) were prescribed for the DCE-MRI, each of which was acquired in 42 seconds. The contrast agent [Omniscan (0.1 mmol/kg); Nycomed-Amersham, Princeton, NJ] was injected manually at start of the fifth frame acquisition and then followed by 10-ml saline flush. All MR images were transferred to a personal computer for post-processing.

Fibroglandular Tissue Segmentation

To avoid the bias coming from the arbitrary ROI selection, we applied a computer-based segmentation algorithm to segment the entire fibroglandular tissues contained in the normal breast using the pre-contrast images of DCE-MRI [15]. Briefly, the segmentation procedures consisted of the following steps: 1) an initial segmentation of the breast region based on V-shape cut using three user-entered anatomic landmarks (thoracic spine and bilateral pectoral muscles); 2) a fuzzy c-means (FCM)–based segmentation algorithm with the B-spline curve fitting to obtain the chest wall boundary; 3) exclusion of skin along the breast boundary by dynamic searching algorithm; 4) removal of non-uniformity in image intensity through bias field correction based on the adaptive FCM; 5) differentiation of the fibroglandular tissue from the surrounding fatty tissue using an FCM-based clustering method. An experienced operator performed the segmentation for all subjects included in this study.

Measurement of BPE

BPE was defined as the average of the contrast enhancements measured from all pixels contained with the segmented fibroglandular tissue. BPE indicated a percent (%) increase of enhancement after